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No. 90-476

IN THE

SUPREME COURT OF THE UNITED STATES

OCTOBER TERM, 1990

WYETH-AYERST LABORATORIES DIVISION OF AMERICAN HOME PRODUCTS CORPORATION,
Petitioner,

v.

MICHELLE GRAHAM, an Infant under the age of 18 who sues by her Parents, Guardians and Next Friends, Charles Graham and Tammy Graham,
Respondent.

PETITIONER'S REPLY BRIEF

Albert K. Knopp
Wayne C. Dabb, Jr.
Mary M. Bittence
BAKER & HOSTETLER
3200 National City Center
Cleveland, OH 44114
(216) 621-0200

Michael T. Scott
Counsel of Record
REED SMITH SHAW & MCCLAY
2500 One Liberty Place
Philadelphia, PA 19103
(215) 851-8100

Hedy M. Powell
Legal Division
WYETH-AYERST LABORATORIES
Post Office Box 8299
Philadelphia, PA 19101
(215) 971-2660

Counsel for Petitioner

November 14, 1990

PACKARD PRESS / LEGAL DIVISION, 1617 JFK BOULEVARD, PHILA., PA. 19103 (215) 563-9000

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MICHELLE GRAHAM, an Infant under the age of 18
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Charles Graham and Tammy Graham,
Respondent.

On Petition For A Writ Of Certiorari To
The United States Court of Appeals
For The Tenth Circuit

PETITIONER'S REPLY BRIEF

ARGUMENT

I. THE PETITION IS NOT PREMATURE.

The questions presented by the Petition are ripe for review. Whether a lay jury may overrule the judgment of the Federal Food and Drug Administration ("FDA") and its Center for Biologics Evaluation and Research on issues of optimum vaccine design and proper vaccine labeling is "fundamental to the further conduct of the

case" and should be reviewed now. *United States v. General Motors,* 323 U.S. 373, 377 (1945).

Where a judgment of a court of appeals is otherwise appropriate for review by writ of certiorari, the fact that the court of appeals has remanded the case to the district court for trial (or retrial) does not preclude review. Indeed, several of the pre-emption cases cited in the Petition were decided by the Court after the court of appeals had remanded the case for trial. *See International Paper Co. v. Ouellette,* 479 U.S. 481 (1987); *Offshore Logistics, Inc. v. Tallentire,* 477 U.S. 207 (1986); *Chicago & North Western Transportation Co. v. Kalo Brick & Tile Co.,* 450 U.S. 311 (1981).[1]

Respondent's reliance on Supreme Court Rule 11 is misplaced. That rule applies only to petitions filed "before judgment is given" in the court of appeals. Its purpose is to ensure that only in the most extraordinary cases will this Court decide a case which has not yet been addressed by the court of appeals. Petitioner seeks review of the judgment already entered by the Tenth Circuit addressing and rejecting the pre-emption argument after a full trial. Rule 11, therefore, has no applicability here.[2]

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1. A brief examination of the cases decided by the Court last term in a variety of areas reveals numerous cases where the court of appeals had remanded the case to the district court for trial, but certiorari was nevertheless granted because of the importance of the issues and/or to resolve a conflict among the circuits. *See, e.g., Franchise Tax Board v. Alcan Aluminum Ltd.,* 110 S. Ct. 661 (1990); *W. S. Kirkpatrick v. Environmental Tectonics Corp.,* 110 S. Ct. 701 (1990); *Atlantic Richfield Co. v. USA Petroleum Co.,* 110 S. Ct. 1884 (1990); *Port-Authority Trans-Hudson Corp. v. Feeney,* 110 S. Ct. 1868 (1990); *General Motors v. United States,* 110 S. Ct, 2528 (1990); *Lujan v. National Wildlife Federation,* 110 S. Ct. 3177 (1990).

2. Also lacking in merit is respondent's suggestion, based on *American Construction Company v. Jacksonville T & K W R Co.,* 148 U.S. 372, 384 (1893), that the Petition must be denied in the absence of "extraordinary inconvenience and embarrassment to the

In light of the importance of the issues presented and the conflict between the judgment below and that in *Hurley v. Lederle Laboratories,* 863 F.2d 1173 (5th Cir. 1988), the Court can and should grant certiorari at this stage. Resolution of the applicable pre-emption principles now will not only obviate the need for a lengthy and unnecessary retrial, but will also provide necessary guidance on a fundamental threshold issue in numerous other pending (or yet to be filed) vaccine cases.[3]

II. THE CONFLICT BETWEEN THE JUDGMENT BELOW AND *HURLEY* SHOULD BE RESOLVED.

With respect to the labeling/warning issues, the conflict between the judgment below and *Hurley, supra,* is clear and direct. In vacating summary judgment in *Hurley,* the Fifth Circuit remanded with the direction that "the only question that can be presented to the jury consistent with the federal regulatory scheme is whether the manufacturer withheld . . . information that would have changed the FDA's decision" on the appropriate warning. 863 F.2d at 1179-80, App. at 116a-117a.

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conduct of the cause." The Court enunciated that standard in the context of "a decree of the Circuit Court of Appeals on appeal from [an] interlocutory order." *Id.* As evidenced by the numerous cases cited at n.1, *supra,* it has no applicability to a case such as this where trial has been held, final judgment has been entered in the district court, and judgment has then been entered in a court of appeals.

3. Respondent makes much of the fact that certiorari was denied in *Abbot v. American Cyanamid Company,* 844 F.2d 1108 (4th Cir. 1988), *cert. denied,* 488 U.S. 908 (1988). There are no adverse inferences properly drawn from denial of the petition in *Abbot. See, e.g., United States v. Carver,* 260 U.S. 482, 490 (1923). As Justice Brennan once explained, a denial of certiorari means "only that the petition for review did not get four votes and it means absolutely nothing more . . . . The Court may well take the very next case raising the same question and reach a different result on the merits." Brennan, State Court Decisions and the Supreme Court, 31 Penn. Bar. Assn. Q. 393, 402-03 (1960).

This "special procedure" was justified, said the court, by the need to give DTP "manufacturers . . . assurance that if they follow certain prescribed procedures, such as including an FDA-approved warning, they are complying with the law." 863 F.2d at 1180, App. at 117a.[4] With regard to the design defect issue, the Fifth Circuit did not decide the issue, but stated that it appeared "likely" that the same analysis should apply and left it to the district court to decide the question in the first instance.

The terms of the remand in the instant case are in stark contrast to the decision in *Hurley*. The Tenth Circuit's blanket rejection of the pre-emption doctrine confers on the jury in the retrial the same unfettered freedom to second-guess the FDA as the first jury enjoyed. Petitioner is totally foreclosed from raising the pre-emption defense in the retrial.[5] The "special procedure" adopted by the Fifth Circuit is completely and prejudicially absent from the Tenth Circuit's remand. The conflict between the Fifth and Tenth Circuits as to the proper issues to be put before the jury in cases such as this should be resolved by the Court.[6]

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4. Respondent seeks to dilute the effect of *Hurley* by pointing to what is described as a "testing" claim (Br. In Opp. at 2, 10-11). This "testing" claim is in reality respondent's warning/labeling claim, for it amounts to nothing more than the assertion that DTP labels should (contrary to the FDA's determination) list the measured quantity of endotoxin in each vial.

5. The district court is, of course, fully bound by the terms of the Court of appeals' remand. *See, e.g., Rutherford v. United States,* 806 F.2d 1455, 1459-60 (10th Cir. 1986).

6. Respondent's suggestion that the Fifth Circuit's approach to pre-emption has been uniformly rejected by the district courts is misleading. The district court opinions in both *Abbot* and in *Hurley* itself went further in recognizing pre-emption than did the Fifth Circuit. Moreover, all of the cases cited by respondent (Br. In Opp. at 20, n.1) were decided prior to the Fifth Circuit's opinion in *Hurley*. Since *Hurley* was decided, there have been no district court opinions rejecting the "special procedure" adopted by the Fifth Circuit. Finally, the cases respondent cites were all decided on summary judgment motions without benefit of the full factual

III. THE NATIONAL CHILDHOOD VACCINE INJURY COMPENSATION ACT NEITHER DIMINISHES THE IMPORTANCE OF THIS CASE NOR ALTERS THE FOUNDATION WHICH SUPPORTS CONFLICT PRE-EMPTION.

A. THIS CASE PRESENTS IMPORTANT PUBLIC POLICY ISSUES.

Respondent, citing the filing of claims under the Vaccine Compensation Act ("Act"), would have the Court deny the Petition as unimportant because it deals "only with the narrow concerns raised by old, pre-Act claims." (Br. In Opp. at 19.) That argument has glaring deficiencies.

First, notwithstanding the Act, there remain dozens of existing lawsuits where plaintiffs and their attorneys — undoubtedly cognizant of the $15 million verdict entered in this case — have, as respondent has, elected to forego the Act's compensation-based remedies and "capped" attorneys' fees for the opportunity to take their design defect and inadequate warnings claims to a jury.[7]

Second, the Act only applies to certain childhood vaccines listed in the statute.[8] All vaccines carry some

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development which here establishes the impossibility of dual compliance with both the federal and state demands.

7. Even those claims which have been filed under the Act to date may become new, or reinstituted, lawsuits once proceedings under the Act have run their course. Filing under the Act is not a preclusion, only a prerequisite, to suits for immunizations administered on or after the Act's effective date. 42 U.S.C. §§300aa-21, 300aa-11(a)(2)(A) (1990). Plaintiffs in such new or reinstituted suits will undoubtedly argue that the alleged injuries were *avoidable* if a differently designed vaccine had been utilized (*see, e.g.*, Br. In Opp. at 6) and that their design defect claims are, therefore, viable notwithstanding the Act. Application of conflict pre-emption principles in the case at bar will dispose of any such arguments in both pre-Act and post-Act suits.

8. In addition to DTP, it covers measles, rubella, polio and mumps vaccines. It does not cover other currently-licensed vaccines such as those for influenza, anthrax, cholera, tuberculosis and

risk of adverse reaction. Striking the optimum balance between efficacy and risk is at the heart of the FDA's regulatory functions. The question of whether juries will be allowed to reject the FDA's judgments and award damages will continue to be of critical importance to the accomplishment of federal public health policies through the use of existing vaccines and to the willingness of manufacturers to make the investments necessary to develop and secure approval and licensure of new vaccines.

B. CONFLICT PRE-EMPTION'S FOUNDATION IN THIS MATTER CONSISTS OF PRIOR FEDERAL STATUTES.

Respondent's principal (if not, only) argument on the merits is that Congress, in passing the Act, has precluded the application of pre-emption principles in any case involving a pre-October 1, 1988 immunization. The statutory language on which respondent relies, however, does not even purport to address the conflict pre-emption issue raised by the Petition. The language respondent quotes simply recites that state – rather than federal – law provides the substantive basis for a claim arising from a pre-October 1, 1988 immunization. It does not purport to address the application of the Supremacy Clause where state tort law concerning the design and labeling of licensed prescription biologicals such as DTP comes into direct conflict with existing federal law, to wit, the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§301 *et seq.,* the Public Health Service Act, 42 U.S.C. §§201 *et seq.,* and their predecessor Acts.[9]

NOTES *(Continued)*

typhoid. Nor does it apply to any vaccine which a manufacturer might, in the future, consider developing or marketing, including, most significantly, an AIDS vaccine, any one of which designs could be declared defective although FDA licensed.

9. To the extent respondent relies on Congress' "assumptions" in 1986 regarding the pre-emptive effect of earlier legislation with

When Congress intends to broadly preserve any existing state law remedies notwithstanding the potential for inconsistency with federal law, it knows how to do so by means of explicit "savings clauses."[10] The language in the Act comes nowhere near being the explicit "savings clause" that respondent would like it to be. But, even more importantly, any such "savings clause" would have little bearing on the proper application of conflict pre-emption principles. Where, as here, it is impossible to comply with both state law and federal law regarding the design and labeling of DTP vaccines, the state law is pre-empted, whether or not Congress expressly intended there to be pre-emption.

Respondent continually ignores the fact that the pre-emption which applies in this suit is not "express"

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respect to a 1980 immunization (Br. In Opp. at 17-18), such reliance is especially ill-founded. This Court has reasoned that "subsequent legislation usually is not entitled to much weight in construing earlier statutes." *Mattz v. Arnett,* 412 U.S. 481, 505 n.25 (1973), *citing United States v. Southwestern Cable Co.,* 392 U.S. 157, 170 (1968). "The views of a subsequent Congress form a hazardous basis for inferring the intent of an earlier one." *Russello v. United States,* 464 U.S. 16, 26 (1983), *quoting United States v. Price,* 361 U.S. 304, 313 (1960).

10. In the Clean Water Act, 33 U.S.C. §§1251 *et seq.,* for example, Congress specified that: "Except as expressly provided . . . nothing in this chapter shall . . . be construed as impairing or in any manner affecting any right or provision of the States with respect to the waters . . . of such states." 33 U.S.C. S1370. *Also see* 33 U.S.C. §1365(e). Similarly, the National Traffic and Motor Vehicle Safety Act of 1966, 15 U.S.C. §§1381 *et seq.,* provides that compliance with federally-mandated safety standards does "not exempt any person from any liability under common law." 15 U.S.C. 1397(c). The Death On The High Seas Act, 46 U.S.C. §§761 *et seq.,* provides that "the provisions of any State statute giving or regulating rights of action or remedies for death shall not be affected by this chapter." 46 U.S.C. §767. The Interstate Commerce Act has long provided that nothing in the Act "shall in any way abridge or alter the remedies now existing at common law or by statute, but the provisions of this act are in addition to such remedies." 49 U.S.C. §10103.

pre-emption or "occupation of the field" pre-emption, but conflict pre-emption. This Court and the lower courts have consistently recognized the viability of conflict pre-emption principles even in the face of explicit savings clauses such as those discussed in note 10, *supra. See International Paper Co. v. Ouellette,* 479 U.S. 481 (1987) (Clean Water Act); *Offshore Logistics, Inc. v. Tallentire,* 477 U.S. 207 (1986) (Death On The High Seas Act); *Chicago & North Western Transportation Co. v. Kalo Brick & Tile Co.,* 450 U.S. 311 (1981) (Interstate Commerce Act); *Texas & Pacific Railway Co. v. Abilene Cotton Oil Co.,* 204 U.S. 426 (1907) (Interstate Commerce Act); *Taylor v. General Motors,* 875 F.2d 816 (11th Cir. 1989), *cert. denied,* 110 S. Ct. 1781 (1990) (Motor Vehicle Safety Act).

This Court applied conflict pre-emption under the Federal Food and Drugs Act of 1906 in *McDermott v. Wisconsin,* 228 U.S. 115 (1913). There, Wisconsin law imposing labeling requirements for syrup was held to be pre-empted because it conflicted with the obligations imposed by federal law. The conflict between state and federal obligations in the instant case is no less direct and *McDermott* is controlling. Nothing in the Act alters the requirement that state law "which has come into collision" with federal law must yield. *Gibbons v. Ogden,* 22 U.S. (9 Wheat) 1 (1824).

IV. RESPONDENT'S COUNTER-STATEMENT IS NEITHER ACCURATE NOR GERMANE TO THE QUESTIONS PRESENTED

Respondent's counter-statement of fact is essentially the same as that contained in her brief in the court of appeals. In its effort to disparage petitioner's motives and conduct, it reflects minimal fidelity to the record, a

point extensively documented by petitioner in its Reply Brief in the Tenth Circuit.[11]

In any event, the proper application of the preemption doctrine does not turn on the weight or credibility of such evidence. Respondent seems to assume that if a genuine factual dispute of some sort can be created, then the issue must be given to the jury. She thus goes to great lengths to present to this Court every conceivable argument which can be mustered in support of the alleged superiority of the various alternative pertussis vaccines compared to the whole cell vaccine (Br. In Opp. 2-12).[12] The task of weighing and evaluating the scientific evidence on optimum design and labeling has, however, been vested in the FDA. It is no more the proper function of a jury, than it is of this Court, to determine whether a whole cell or an acellular pertussis vaccine is the best means of preventing pertussis. *See Jacobson v. Massachusetts,* 197 U.S. 11 (1905).

The fact which is controlling here is not in any doubt and it is this: Petitioner is being sued for failing to market a product which it could not lawfully have sold and for marketing a DTP product which was approved by the FDA, which Petitioner was licensed to market

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11. Cognizant of this Court's requirement that factual misstatements be identified or waived (Sup. Ct. Rule 15.1), as well as the applicable time and page limitations, we have attached hereto as a Supplemental Appendix the Statement of Facts made in the respondent's Tenth Circuit Brief and that portion of the petitioner's Tenth Circuit Reply Brief documenting the misstatements therein. Supp. App. 252a-278a.

12. Respondent's argument concerning the alleged superiority of the Eli Lilly non-whole cell vaccine and petitioner's failure to market such a product deserves special attention. That vaccine provided the foundation for petitioner's application to the FDA in 1982 for a license to market a non-whole cell vaccine. The FDA, citing evidence that the non-whole cell vaccine was inferior to the whole cell on both efficacy and safety grounds, denied the request. Tr. 659, 3098-99; U.S. *Amicus* Br. at 92a-94a.

and which is essential to preservation of the public health. In the area of biologics, the FDA is far from a "passive agency" propounding "minimum standards." It, together with the National Institutes of Health and Centers for Disease Control, is at the center of vaccine research, innovation and evaluation.[13] The FDA has firmly concluded that the whole cell pertussis vaccine is superior – not inferior – to the various unproven alternatives and, under the Supremacy Clause, a jury applying state tort law should not be free to reject that determination.

V. CONCLUSION

For the foregoing reasons, the Petition For A Writ Of Certiorari should be granted.

Respectfully submitted,

Albert K. Knopp
Wayne C. Dabb, Jr.
Mary M. Bittence
BAKER & HOSTETLER
3200 National City Center
Cleveland, OH 44114
(216) 621-0200

Michael T. Scott
Counsel of Record
REED SMITH SHAW
& MCCLAY
2500 One Liberty Place
Philadelphia, PA 19103
(215) 851-8100

Hedy M. Powell
Legal Division
WYETH-AYERST
LABORATORIES
Post Office Box 8299
Philadelphia, PA 19101
(215) 971-2660

Counsel for Petitioner

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13. *See* U.S. *Amicus* Br., App. at 94a-102a; Agenda For Sixth International Symposium On Pertussis, App. at 238a-251a. The acellular vaccine used in Japan, for example, was developed in large part by Dr. Yugi Sato while working at the FDA on a fellowship.

SUPPLEMENTAL APPENDIX

NO. 88-1337

UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

MICHELLE GRAHAM, an infant under the age of eighteen who sues by her parents, guardians, and next friends, Charles Graham and Tammy Graham,

APPELLEE,

vs.

WYETH LABORATORIES DIVISION OF AMERICAN HOME PRODUCTS CORPORATION,

APPELLANT

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF KANSAS

BRIEF OF APPELLEE

I.
STATEMENT OF FACTS

Plaintiff Michelle Graham, now eight years old, suffers from encephalopathy (brain damage) which has rendered her a severely multihandicapped child, including gross mental retardation and severe physical disabilities. Plaintiff contended at trial, and the jury so found, that defendant Wyeth caused Michelle's brain damage (encephalopathy) by knowingly manufacturing and marketing a vaccine of unpredictable, lethal toxicity—a toxicity that could have been easily avoided by readily available technology (Doc, 152, Inst. No. 8; Defendant's Attachment p. A95-96). Plaintiff did not contend that the Wyeth DPT vaccine was not efficacious or that defendant should be liable for marketing an unavoidably unsafe vaccine which nevertheless causes injury (TR 5, 5594). Plaintiff did not contend that DPT vaccine should be taken off the market. On the contrary, plaintiff conceded that if the risk of injury was *unavoidable,* then the benefits of the vaccine outweighed its risks in a cost-benefit analysis *(Id.)* The issue in this case was, therefore, quite narrow. Could defendant Wyeth have made its vaccine safer with the existing technology available at the time Michelle Graham received her shot? As the following discussion of the medical and scientific testimony on DPT vaccine will show, plaintiff proved to a reasonable scientific certainty that Michelle Graham's brain damage could have been avoided had defendant Wyeth utilized the existing scientific technology to improve its DPT vaccine.

It is apparent that defendant seeks to retry the factual issues which have already been fully litigated before a jury which weighed and resolved these factual disputes in favor of Michelle Graham. For this reason, plaintiff has devoted a substantial portion of her brief to the review of the evidence adduced in her favor at trial.

The product at issue in this case is a trivalent vaccine commonly referred to as "DPT" vaccine. The vaccine is designed to immunize children against diptheria (D), tetanus (T) and pertussis (whooping cough) (P) (TR 222-23). This vaccine is derived from the disease organisms themselves which, when injected into the human system, trigger an intricate antibody response which serves to protect the vaccine recipient from each of the three target diseases.

1. All three bacteria in the DPT vaccine produce toxins, or poisons, which can cause severe injury in the human body. In order to purify the vaccine to the greatest extent possible and thereby reduce the harmful effects of these toxins, the toxins can either be removed or their toxicity destroyed through the artificial means of toxoiding. Both the diptheria and tetanus components of the Wyeth DPT vaccine are toxoids. The Wyeth pertussis vaccine, however, contains whole cells of *Bordetella pertussis* bacteria from which known harmful toxins have not been removed nor their poisonous effects blunted by artificial toxoiding. Thus, the Wyeth pertussis component is known as a "whole cell" vaccine (TR 222-23, 915-916; PX 620 and 19C).

2. Pertussis bacteria produce two poisonous substances known as endotoxin and exotoxin. Both poisons are contained in Wyeth whole cell pertussis vaccine and cause severe injuries to the human system in their unaltered states (TR 222-23, 244-48, 256-58, 267, 300-304, 857, 893-95). Endotoxin is a highly-virulent poison, one of the most highly feared substances in medicine (TR1010). It is a well-known neurotoxic agent that is known to cause injury to the brain and is the component in Wyeth DPT vaccine responsible for brain damage sustained by children following vaccination (*Id.;* PX 17B, 128). The adverse effects of Wyeth DPT on the human body range in severity from local reactions in the tissue where it is injected, such as swelling, pain and inflammation, to systemic reactions including fever,

seizures, shock, encephalopathy and death (TR 873, 893-95, 1010, 300-306). These toxic effects have been well-known in the scientific and medical communities for over 40 years (TR 248-49, 258-262, 298-99, 304-05; PX 19B, 173; DX 161, 44). Defendant Wyeth by its own admission has known since the mid-1950's that endotoxin is unnecessary to confer immunity and that it can be removed from the vaccine without destroying its effectiveness (TR 217-18, 249-52, 3508-09; PX 96, 35, 66, 41).

3. Exotoxin is believed to aid in conferring immunity in the vaccinated child and is, therefore, one of the necessary elements of pertussis vaccine. However, in a non-toxoided state, exotoxin is also highly injurious to the human system, affecting, among others, the lymphatic, vascular, and central nervous systems (TR 217-18, 249, 256-58, 1083). Combined with endotoxin, exotoxin has a potentiating effect, that is, its effects on the body permit and enhance the injuries to the brain caused by endotoxin (TR 256-258, 300-307, 316-17, 936). The harmful effects of exotoxin can be substantially eliminated by toxoiding the exotoxin with a simple chemical process. This fact has been known for 50 years (TR 219) and in use at least since 1937 (TR 252, 426-30, 917; PX 19B).

4. In sum, the neurotoxicity of the Wyeth whole cell pertussis vaccine is avoidable, unnecessary to protect children against whooping cough, and poses an unacceptable and unreasonable danger of permanent brain damage to children (TR 195, 217-19, 249-252, 258, 262-67, 350, 371, 375-77, 436, 445-46, 463, 475, 786, 917, 942-44, PX 60A-B, 173, 26, 36, 19, 19A-B, 59, 59B).

5. These poisons were injected into the infant plaintiff, Michelle Graham, on March 17, 1980, when she received her first DPT shot with Wyeth's vaccine, and caused her permanent, irreversible brain damage (TR 1570; 1573; 1860). She is "profoundly retarded:" a

severely multihandicapped child who will require custodial and rehabilitative care for the rest of her predicted lifespan of 55 years (TR 1460-61, 1681-82).

HISTORY OF PERTUSSIS VACCINE

6. In 1907, Bordet and Gengou isolated the pertussis organism, a gram negative bacteria. All gram negative organisms contain endotoxin, a substance which is widely recognized as a potentially lethal poison when it invades the human system (TR 242-244). It has been known that the entire whole cell bacteria was not necessary to confer immunity against whooping cough at least since the 1920's (TR 217-18, 249). Defendant Wyeth has been aware of the toxicity of its whole cell vaccine, including its capacity to cause brain damage since at least 1960 (PX 19, 39, 41, 42) and has repeatedly acknowledged the need to reduce that toxicity through toxoiding of exotoxin and removal of endotoxin (PX 42, 39, 41, 19, 19C, 53, 55, 173; TR 249, 298-99). Indeed, Wyeth documents establish that Wyeth scientists have known and understood that endotoxin could be removed from the vaccine and the exotoxin toxoided so as to produce a safer but efficacious vaccine since the mid-1950's (PX 96, 35, 66, 41).

7. In 1947, defendant Wyeth began marketing its whole cell DPT vaccine. This same vaccine product has been produced and marketed by defendant Wyeth, without any substantive change, for the last forty-plus years and is the product injected into Michelle Graham in 1980 (TR 1102). Apart from the universally recognized methods of purification of the whole cell vaccine available to Wyeth throughout the decades, alternative vaccine technologies have existed since at least 1937 (TR 462-27, 917, 943).

8. It has been known for 30 years that only toxoided exotoxin and the "pilli" (small hairs on the outer cell wall) are necessary to confer immunity. The technology

for producing an "acellular," vaccine, that is, a preparation in which the unnecessary components of the cell are removed, was available to defendant Wyeth no later than 1937 (TR 249-252, 917; PX 19B), when Lederle Laboratories applied for a patent of a pertussis vaccine toxoided with formaldehyde and the exotoxin toxicity therefore blunted (TR 917, PX 19B). In fact, the Lederle application was originally rejected by the patent examiner on the ground that it was known to everyone that you could toxoid pertussis vaccine with formaldehyde (TR 917). This same toxoiding process is in use today in a Japanese vaccine which Wyeth executives have hailed as an "unmatched achievement" (TR 436), citing the "stunning epidemiological evidence of the safety and efficacy of the new Japanese vaccines (PX 80).

9. By 1958, Eli Lilly & Co. had developed an acellular, soluble vaccine which defendant Wyeth admits was "superior to all others on the market, including Wyeth's" (PX 66). The Lilly soluble vaccine, Tri-Solgen, showed significantly fewer adverse reactions to whole cell vaccine and no serious effects such as convulsions and brain damage (TR 943). Highly placed Wyeth officers, including Wyeth's president, have repeatedly admitted that the "fairly convincing evidence" established that Lilly Tri-Solgen was "less reactive," a "prestige vaccine" far superior to Wyeth's whole cell vaccine (PX 128, 66, 258, DX 228, DX 161). Through the Lilly process, 90% of the endotoxin was eliminated from the vaccine (TR 390). Lilly Tri-Solgen was greatly preferred in the medical community as a safer product and obtained a vaccine market share of 50%. It was expected that eventually Tri-Solgen would occupy 70% of the vaccine market (TR 389-91; 942-43). However, Lilly ceased marketing Tri-Solgen in 1977, when it chose to leave the vaccine business entirely to pursue other products.

10. By the mid to late 1950's, both defendant Wyeth and the scientific community recognized that the whole

cell vaccine was *avoidably* unsafe and that an acellular vaccine was a "high priority" in order to reduce the vaccine's toxicity and consequent dangers to children (PX 39, 41, 26, 42, 35). The success of the Lilly acellular vaccine as a safer alternative was well-documented and admitted by the executives at Wyeth (PX 96, 36; TR 373-77). In fact, in order to try to compete with Lilly, Wyeth's Dr. Tint applied for patent of an acellular vaccine process in 1960 which became known as Project 77A (PX 19). Dr. Tint admitted in his patent application the necessity for reducing adverse reactions to the whole cell vaccine and proposed a proven effective toxoiding process by which a safer soluble vaccine could be produced (PX 19, 35, 36, 39, 41, 42; TR 380-88). Dr. Tint's proposal to Wyeth to develop the vaccine advised there was a significant problem in the whole cell vaccine and Tint stated in 1957, "It is strange only that presentation of a soluble pertussis product has been so long delayed" (PX 35; TR 379). His soluble vaccine patent was issued in 1962 (TR 383).

11. The Tint vaccine was used by Wyeth in Quadrigen, a proposed vaccine product containing DPT and Salk polio vaccine (TR 384), to compete with the quadruple antigen vaccine on the market by Merck, Sharpe & Dohme. The Merck vaccine contained a safer, less reactive soluble pertussis component as of 1959-60 (PX 663; TR 3055). Unfortunately, the Sabin oral polio vaccine which was developed rendered the Salk vaccine no longer financially competitive and Wyeth abandoned Quadrigen. When it did so, it also shelved the safer Tint pertussis vaccine. The Tint project died from lack of manpower, facilities and financial support. Other projects were viewed as having a "higher priority" (PX 49). Despite the fact that at least two perfected, safer, acellular vaccines had reached the market by 1960, Wyeth continued to lag behind, never deviating from its whole cell product first licensed in 1947 (TR 384-88; PX 49, 41).

12. Twelve years after abandoning the Tint vaccine, Wyeth again took up research of a safer acellular DPT vaccine. In 1973, Dr. Carole Long, a scientist freshly hired out of graduate school, was assigned the task of researching an acellular pertussis vaccine on a part-time basis. She devoted only one-third of her time to DPT research (TR 2943). Yet, in the space of only a few months, Dr. Long reported to her supervisor, Dr. Rubin, she had succeeded in developing an acellular extract. Within one year, Dr. Rubin and Dr. Long recommended that Dr. Long's work be scaled up to determine its viability at a production level (PX 59B, 60A, 60B, 61A, 63). Using the same techniques available since the early 1950's and in use by Lilly, Dr. Long had developed a pertussis extract offering "considerable protection" by September of 1975 (TR 2944, 2947, 2981-82, 2984, 3001, 3005-3007, 3009-10; PX 63, 61A, 61).

13. Dr. Long's extracted antigen, which was very similar to the Japanese vaccine introduced in the late 1970's. repeatedly passed federal potency and toxicity tests (TR 3002; PX 60, 61A). Despite the recommendation of Dr. Long and Dr. Rubin that the Long extract was a potentially successful acellular vaccine with ten-fold less endotoxin, Dr. Long left Wyeth and nothing was done to further her work (TR 460, 464). Instead, Wyeth decided to go after a ready-made acellular vaccine product, the Lilly Tri-Solgen (PX 66).

14. In 1977, Wyeth entered negotiations with Lilly to obtain the rights and technology to make Tri-Solgen, its "prestige" acellular vaccine (PX 66). Ultimately, Wyeth purchased both the Tri-Solgen trademark name and the acellular process, including the Lilly bacterial strains for manufacturing the purified vaccine (TR 392). During these negotiations, Wyeth executives consistently acknowledged the superiority of the Lilly vaccine and the need for Wyeth to convert from the whole cell to the safer acellular vaccine in order to reduce the reports of adverse reactions in the field (PX 66, 67, 69, 49, 53,

128, 142). Scientific investigators reported the Lilly Tri-Solgen to be equally effective but less reactive than the whole cell (PX 258, DX 228, PX 74, 72). Wyeth agreed there was "little doubt" that Tri-Solgen caused less systemic reactions such as fever, vomiting, anorexia, hypotonia, collapse, shock, seizures, central nervous system disorders, and anaphylaxis (PX 128, 149B, 149C; DX 161).

15. Wyeth, however, chose not to manufacture and market the superior and safer Tri-Solgen vaccine. Instead, Wyeth substituted its own seed strains and growth mediums and altered the Lilly manufacturing process so as to reduce the enhanced cost of manufacturing the acellular vaccine (PX 67; TR 393-400).[1]

16. The Lilly Tri-Solgen lay dormant at Wyeth for five years, from 1977 to 1982. During this time, American children, including Michelle Graham, had no choice other than the whole cell vaccine despite the fact that a safer acellular vaccine was owned by Wyeth. Finally, Wyeth sought a license amendment to allow it to substitute its cheaper version of the Lilly vaccine for its whole cell pertussis component and yet still name the vaccine Tri-Solgen (PX 142, 80A). The FDA refused to authorize the vitiated version of Tri-Solgen but strongly advised Wyeth that its new acellular vaccine could be licensed without the Tri-Solgen trademark if Wyeth complied with the usual FDA requirements, removed the endotoxin and toxoided the exotoxin with formaldehyde, the toxoiding method available since 1937 (PX 80A, 66, 109, 142, 67; TR 395-402). Wyeth declined to

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1. The cost of manufacture of the vaccine is "dirt cheap" and can be measured as only a few pennies (TR 398; 1089). The increased cost of an acellular vaccine is approximately five-fold the cost of whole-cell, but even a ten-fold increase would raise the cost of manufacture to only a dollar or two, a price any parent would spend to provide a child with a safer vaccine (TR 398, 1114-15; PX_____).

follow the FDA's recommendation. Although the acellular vaccine could easily have been licensed and marketed using existing technology available to Wyeth at the time it negotiated the purchase of the Lilly vaccine, Wyeth shelved the Lilly vaccine as it had abandoned its efforts to pursue marketing of its own alternative acellular vaccine (TR 395, 400-402). Neither Tri-Solgen nor Wyeth's version of it have ever been offered to American children by Wyeth.

17. The improvements suggested by the Bureau of Biologics (FDA) could easily have been achieved by Wyeth. Indeed, Dr. Wainwright and other executives at Wyeth held a pertussis vaccine meeting during which they emphasized "the urgency of developing a new pertussis vaccine in a relatively short period of time" (PX 80A). The group acknowledged that making the changes indicated by FDA to Wyeth's existing acellular vaccine was "the quickest and easiest approach" to meeting the urgent need for a new, less reactive pertussis vaccine *(Id.)*. Wyeth failed once again to follow through on this acellular vaccine and called a halt to the project to await the marketing in the U.S. of a new acellular vaccine perfected by the Japanese in the late 1970's, rights to which Wyeth hoped to acquire (PX 80). Wyeth's application for licensure of its acellular "Lilly" vaccine still languishes, "pending," at the FDA awaiting action by Wyeth.

18. The Japanese product for which Wyeth suspended all its efforts towards a safer vaccine is actually a modern distillation of the American knowledge and technology available through the 1960's and 70's (TR 428-29, 446; PX 17, 17B, 17C, 17D). In 1975, two Japanese children died as a result of vaccination with whole cell DPT. As a result, the acceptance of whole cell vaccine by the Japanese public fell dramatically (TR 457). This stimulated the Japanese Ministry of Health to develop and introduce a Japanese acellular vaccine *(id.)*. Dr. Sato of Japan came to the United States to study

vaccine technology and was a Fellow at the National Institute of Health (NIH), an arm of the FDA, in 1978 (TR 455). Based on the technology, information and experience Dr. Sato garnered in the United States, he presented data to the 1978 Pertussis Vaccine Conference held by the Department of Health Education and Welfare. His position paper verified that an acellular protective pertussis antigen could be extracted and purified from the whole cell (TR 786). Wyeth attended this conference and was fully aware of Dr. Sato's successful work with an acellular product (PX 17B).

19. Dr. Sato returned to Japan and utilizing the technology and knowledge gathered in the United States, the Japanese successfully developed an acellular vaccine by 1978 and Japanese children were receiving it by 1981 (TR 457-58; PX 101; TR 460). The Japanese vaccine was hailed by Wyeth as an advancement over Wyeth's whole cell vaccine that was unmatched by anything Wyeth could produce (PX 80). Indeed, Wyeth acknowledged that the "costs of litigation will be much less, perhaps none, with acellular vaccine" based on the Japanese experience of only one doubtful claim for over 15 million doses of vaccine (PX 94). Wyeth signed an exclusive supply and manufacturing agreement in 1982 with the Japanese company, Takeda, for the first generation acellular vaccine in Japan (PX 101). However, Wyeth once again failed to push forward with a safer alternative and never pursued production of the Takeda vaccine (TR 436), even though Wyeth executives admitted "the Japanese [have] proved the efficacy of their vaccine in a way that is quite impossible for us to duplicate" (PX 80). Instead, Wyeth had concluded by 1983 that it was advantageous to wait for the second generation Japanese vaccine of Dr. Sato to become available as it was cheaper and more profitable to make, and estimated the Sato vaccine to be likely to be on the market about two years after the Takeda vaccine (PX

101). As of 1985, Wyeth had still not moved ahead on the Japanese acellular.

20. In 1985, Wyeth began selling its whole cell vaccine to Lederle Laboratories (TR 437; PX 94). Wyeth documents state, however, that Wyeth kept its option open to market the Japanese acellular vaccine because of its potentially high profitability *(Id.)*. That option was never exercised by Wyeth. To date, the only DPT vaccine ever manufactured by defendant Wyeth is the toxic whole cell vaccine administered to Michelle Graham in March of 1980.

21. In addition to all of the safer vaccines available for the 30-40 years prior to Michelle's vaccination, even the whole cell vaccine could be made safer. At the very least, defendant Wyeth was able to toxoid the vaccine with formalin, a process available and effective for over forty years (see *supra.*) Wyeth never availed itself of this simple method of reducing toxicity. Failing that, Wyeth was able to, at the very least, measure the level of endotoxin present in its whole cell vaccine. Lots of Wyeth vaccine placed on the market are greatly variable in their endotoxin levels, thus rendering some lots far more reactogenic, or toxic, than others (TR 198, 279, 295). The toxicity is highly variable batch to batch and lot to lot, thus making the whole cell vaccine unpredictably unsafe (TR 267-68, 279, 295, 1030-32, 1120, 198). The number of adverse reactions, both local and systemic, are correlated to the level of endotoxin in the vaccine; i.e., the higher the level of endotoxin, the greater the risk of injury, brain damage, or death (TR 1035). The Center for Disease Control (CDC) has developed criteria for determining "hot lots," or lots which cause an elevated number of adverse reactions in children (PX 105). In addition, the CDC has conducted its own efforts to track "hot lots" and monitor their reactogenicity in the field (PX 105, 88M). Part of this effort was the attempt to obtain distribution data from vaccine manufacturers so as to compile information which

would aid in identifying potential hot lots and whether Wyeth lots have higher rates of reactions than other DPT manufacturers (PX 88G, 105). CDC information revealed that Wyeth whole cell was reporting out an excessive number of reactions as compared to other manufacturers (PX 105, 88F, 88G, 88M; TR 209-10). Obtaining such distribution data is important because no estimate of reaction rates per lot is possible without knowing where and how much of the lots have been distributed (TR 213-17). Wyeth declined to supply the requested information (PX 88G; TR 213-17).

22. In 1979, several deaths from SIDS (Sudden Infant Death Syndrome) were reported to the CDC from Tennessee which were associated with a single lot of Wyeth whole cell vaccine (Bierly Depo., p. 62). Following this event, Wyeth changed its distribution policy so that no one lot or large portion of it would be distributed to "a single state, county or city health department" (PX 103). The effect of this redistribution was that it decreased the likelihood of an excessive reaction rate to a particular lot being detected to those gathering hot lot information (TR 1844-45). Clusters of adverse reactions would no longer occur and authorities would not be alerted to the fact that there might be something wrong with a lot of vaccine (TR 805). Likewise, such a distribution policy increases the likelihood of reporting error as well as failure to report reactions (TR 345). These realities make it even more essential for the agency collecting reaction rate data to have access to distribution information from the manufacturer. Only with this information is the CDC capable of accurately identifying potential hot lots and taking action to prevent their distribution. The DPT shot received by Michelle Graham came from just such a "hot lot" (TR 490-93, 465, 470; PX 105, 617).

23. Given the propensity of Wyeth whole cell to fluctuate enormously in toxicity, as well as its tendency

to increase in toxicity after release from the manufacturer, testing for endotoxin levels is imperative (TR 800-803, 1042, 490-93).

There is a simple, easily available method of measuring the endotoxin content of each lot or batch of whole cell vaccine, known as the LAL, or limulus test (TR 875-76). The LAL test has long been available, and in fact had been used by Wyeth to measure endotoxin content in the laboratory in 1975-76 (TR 885-86; PX 131). Use of the LAL test would permit Wyeth to measure the level of endotoxin and label each vial as to its endotoxin quantity, thereby providing critical information to treating physicians which would permit them to choose low-toxicity doses of pertussis vaccine for their patients (TR 883, 906). Further, such endotoxin testing would enable both the company and the medical community to correlate the rate of reactions to the endotoxin level, thus providing a valuable control mechanism (TR 891, 905; PX 321). Such monitoring and reporting of endotoxin levels would be of great benefit in understanding the vaccine's known toxic effects and would permit the development of testing data so as to monitor and prevent adverse reactions in children (TR 905-907, 891, 838). The use of the LAL test to quantify endotoxin was recommended to manufacturers by Dr. Geier in 1978, long before his involvement in DPT litigation (PX 321).

24. Most physicians have no idea whatsoever that there is endotoxin in Wyeth pertussis vaccine and none have any idea as to the quantity of endotoxin present (TR 874). Virtually everything in medicine must be certified as "endotoxin-free" by law. This is not the case with DPT vaccine, even though FDA regulations require manufacturers to advise on the package label if DPT contains "known sensitizing substances" and require all unnecessary pyrogens or toxins to be removed from drug and vaccine products. Both endotoxin and exotoxin are known sensitizing substances. Endotoxin is a pyrogenic

toxin unnecessary to the vaccine (TR 304, 837-875). *See* 21 C.F.R. 600.3(r), 610.13, 610.61 (l) and (m). Defendant Wyeth, however, has never labeled any of its DPT vaccine to indicate either the presence of endotoxin or quantified its amount (TR 907). These failures to toxoid the whole cell, test for endotoxin content and label the vaccine accordingly, rendered the vaccine unreasonably dangerous and created severe risks which were easily avoidable (TR 942-44, 1014, 1021, 217-18, 371, 377, 426-30, 475, 801, 807, 830; PX 35, 41, 88E).

THE WYETH WARNING

25. In 1980, Wyeth whole cell DPT vaccine was accompanied by the following warnings in the package insert:

> The below-listed serious, and occasionally fatal, reactions have been r*eported following* administration of pertussis-vaccine-containing preparations. The incidence of these reactions is *unknown,* but they seem to be exceedingly rare. Should such reactions occur, further immunization is contraindicated.

(PX 620) (emphasis added). Among the reactions listed are "collapse followed by prolonged prostration and a shock-like state," "isolated convulsion(s) with or without fever," and "frank encephalopathy with changes in the level of consciousness, focal neurological signs and convulsions with or without permanent neurological and/or mental deficit." *(id.)* Central nervous system disorders, cardiovascular accidents (such as the "stroke" suffered by Michelle Graham), permanent brain damage and death are well known effects of the endotoxin contained in the Wyeth whole cell vaccine (TR 873, 893-95, 1010, 300-306, 248-49, 258-62, 298-99, 1441-43, 1449, 1453, 1473, 1512, 1521, 1570-74, 1589; PX 60A, 60B, 88G, 72, 88B, 149E, 149F, 682, 681, 679, 677, 683, 684, 693, 173, 205, 238, 258, 300, 302, 333, 376, 458, 557, 621, 641, 707, 711 712, 173, 19B).

26. The language of the insert advises, and the defense position at trial was, that there is no cause and effect relationship between the enumerated adverse reactions and DPT vaccine. The package insert states that such reactions "have been reported." Any association, the defendant argues, is only a "temporal relationship" between DPT and severe system reactions such as convulsions, brain damage, or encephalopathy (Brief for Appellant, pp. 5-6). The evidence, however, established that Wyeth's whole cell vaccine *causes* these reactions and that Wyeth knew it (TR 305-307, 340-42, 370-71, 463, 477; PX 300, 302, 88B, 149B, 26, 59B). As Wyeth's Dr. Bierly admitted three and a half years prior to Michelle's vaccination, "the pertussis component of DPT preparations is considered by most *to be responsible* for the local and systemic reactions which may follow their administration" (PX 128). This fact was reported by Wyeth executives and scientists as early as 1960 and was abundantly documented in the medical literature and Wyeth documents over the years (PX 149E, 19, 26, 35, 41, 42, 173, 238, 620, 258, 302, 60A, 60B; TR 893-94).

27. Wyeth knew that the incidence of serious reactions caused by whole cell DPT was *not* "unknown," and that the scientific literature established that these adverse reactions were not "exceedingly rare." Indeed, internal documents reflect that Wyeth predicted and "expected" seizures in one of every 15,000 doses and had been informed by scientists involved in pertussis research that the reaction rate was much higher: 1 in 300 of generalized seizures (PX 72, 333, 17A, 571). Adverse reactions to DPT are notoriously underreported and, therefore, even these figures are distorted and the incidence rate is likely much higher (TR 1013-15). A British study in the late 1970's (known as the NCES), focused on especially severe systemic reactions and found that such reactions occurred once in every 110,000 doses of whole cell DPT and permanent brain

damage in one of every 310,000 doses. As British children receive three doses, this translated to one severe systemic reaction in 34,000 vaccinated children and permanent brain damage in one of every 110,000 (PX 17C). The NCES study is the main study quoted by the scientific community as establishing that the risk of encephalopathy (brain injury) is increased significantly by DPT vaccine (TR 1073). It showed to a 99.9% certainty that the risk of brain damage within 72 hours of the shot increased 440% (TR 1070-72; PX 17C).

28. A Swedish study by Strom from 1959-65 showed the risk of cerebral reactions (reactions involving the brain and other central nervous system organs) was one in 3600 vaccinations given (PX 621; TR 1003-1007). Significantly, the rate did not take into account the fact that children were vaccinated more than once in that period, so the risk to each child would actually be much greater. This fact is born out in the Cody-Baraff study (PX 17A) in the United States which reported a risk rate of one in 300. The final published results of the United States study established the risk of seizures was one in 1750 doses and the risk of shock to be one in 1700-1800 doses (PX 17A, 333; TR 936, 1014). American children receive five doses of DPT vaccine, thus the risk is actually five-fold greater per child. Thus, the term "exceedingly rare" is not only inaccurate, it is deceptively misleading to physicians (TR 1108, 936).

29. The Wyeth package insert was grossly deficient in several aspects: it failed to advise physicians of the presence of endotoxin and its quantity (TR 907-08); it failed to advise of the presence of histamine sensitizing factors (TR 807, 830); it stated the reported adverse reactions, including encephalopathy, or brain damage, "were reported following" DPT vaccination, although a clear cause and effect relationship was admitted by Wyeth and well-documented in the literature (TR 305-307, 340-42, 370-71, 463, 477; PX 300, 302, 88B, 149B, 26, 59B); it advised physicians the reaction rate was

"unknown." but "exceedingly rare" when, in fact, the incidence rate was well-documented and not in the least rare (see *supra*). These proven insufficiencies in the package insert rendered the warnings inadequate (TR 936-40).

WYETH TESTING RECORD

30. The FDA imposes several "minimum requirements" on the Wyeth whole cell DPT vaccine. Only one directly relates to the safety and toxicity of the vaccine—the mouse toxicity, or weight gain, test (MWG). The MWG, quite simply, requires that twenty mice be weighed after injection with DPT. If the mice, when weighed as a lot, gain weight according to a specified schedule, the vaccine "passes;" if the mice fall to gain, the vaccine falls (PX 62). Wyeth routinely stored the excessively toxic, failed lots or mixed them with other passed lots and retested until the diluted lot passed the toxicity test (TR 820-23, 197-99, 753, 793-94, 884). It has long been well recognized by the industry (including Wyeth) and the scientific community that the mouse weight gain test is of no predictive value as to the vaccine's safety or toxicity to children (*Id.;* PX 691, 409). Despite this fact, Wyeth has never used any of the various other proven, effective methods to test for toxicity in its commercial vaccine administered to the children of this country, although the company used alternative tests for endotoxin in their own laboratory (TR 812, 828-31, 895, 875-76, 334, 351, 885-86, 198-99; PX 131).

31. Wyeth never performed any tests to correlate the relationship between encephalopathy and its whole cell vaccine although numerous means were available to test endotoxin levels and its effects on the central nervous system (TR 220-21, 323-24, 331-32, 891-93, 905-06, 994, 1019, 940-41, 3461). Wyeth has also never conducted tests or research to determine the effects of

endotoxin on the body (TR 4980). Further, Wyeth has never conducted studies to determine reaction rates to its pertussis vaccine nor even correlated the adverse reaction reports it does receive to the toxin levels in its vaccine (TR 220, 339, 401, 804, 812, 940, 994). Such follow-up studies are critical for determining accurate reaction incidence rates (TR 1013-14, 1021).

32. One obvious testing mechanism available to Wyeth to determine the effects of its vaccine on the central nervous system would be to autopsy the mice used in the MWG to detect brain changes. The Company has never performed this simple procedure, even on the mice that have died from injection of DPT (TR 220-21). Although numerous reports of adverse reactions, including brain damage and death, have been received by Wyeth from the scientific and medical communities, Wyeth has never followed up these reports to discover the long term effects of the vaccine or, for that matter, requested laboratory test results in order to either confirm or refute the association of the reported reaction to its vaccine (TR 4957, 5015, 5069-70).

33. Also, it has been known for many years that certain children are particularly sensitive to pertussis vaccine and more susceptible to injury than others (TR 275, 310). Children can be tested for sensitivity to the vaccine by a simple skin test. The fact that children can be tested to determine sensitivity has been known to Wyeth at least since 1953, but the Company has never advised the public of it, attempted to conduct its own sensitivity testing, nor recommended it to physicians for use prior to vaccination (TR 380-82, 258, 275, 232-34).

34. Additional testing methods were also available to Wyeth to determine the vaccine's effects in children which Wyeth never investigated or pursued. One is EEG testing of children prior to and after immunization which would measure brain wave changes associated with pertussis vaccination. Such an EEG study was performed by Dr. Low in 1955, which established the

viability of such clinical testing and showed that many children did have abnormal brain wave changes following immunization with DPT (PX 205; TR 323-31).

35. Finally, it is a well recognized fact that the endotoxin levels in pertussis vaccine increase during storage and as a function of handling (TR 800-803, 1042). The leaking or release of toxins from the whole cell over time can result in a lot with sufficient increased toxicity to fail the MWG even though it has already passed FDA toxicity testing and been cleared for distribution (TR 279). Yet, Wyeth has never performed testing of pertussis vaccine to measure the increase of toxicity during storage or to determine if toxin levels reach dangerous levels with handling or during its shelf life (TR 279, 493, 801). The toxicity of Wyeth pertussis vaccines is therefore unpredictable, variable and unsafe for injection in children (TR 801). It has also been demonstrated that different mouse strains react differently to the toxins so that a vaccine lot might pass the MWG with one mouse strain and fail with another. Wyeth documents illustrate that when the vaccine failed toxicity testing using one mouse strain, Wyeth would retest, substituting another mouse strain which produced a passed toxicity test (TR 486-490, 813-816). The vaccine thus varies widely batch to batch and lot to lot without adequately controlled testing to achieve uniformity of testing results (TR 490-93).

NO. 88-1337

IN THE UNITED STATES COURT OF APPEALS FOR THE TENTH CIRCUIT

MICHELLE GRAHAM, an infant under the age of eighteen who sues by her parents, guardians, and next friends, Charles Graham and Tammy Graham,

APPELLEE,

vs.

WYETH LABORATORIES DIVISION OF AMERICAN HOME PRODUCTS CORPORATION,

APPELLANT.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF KANSAS

REPLY BRIEF FOR APPELLANT

INTRODUCTION.

The Brief of Appellee contains no less than 155 inaccurate record citations. This glaring perversion of the record can be attributed at best to overzealous advocacy and at worst to deliberate misrepresentation. It has resulted in a presentation which by "factual" misstatement, innuendo, and half-truths creates the illusion that Wyeth and, inferentially, other manufacturers were, and are, making a product that they knew could cause brain damage in children and, further, that they

deliberately chose to ignore available "inventions" which would have resulted in a "safer" vaccine. This is simply not the truth and to this very day the only vaccine which is made and distributed in this country is the whole cell vaccine, made in a manner approved by the Congressionally mandated watchdog of the pharmaceutical industry, the FDA.

Although space limitations preclude a detailed response to each of the inaccuracies, the following tables present, in summary form, the magnitude and effect of plaintiff's misrepresentations:

STATEMENTS WHICH ARE NOT SUPPORTED BY PLAINTIFF'S RECORD CITATIONS.

Statement	Citations	Comments on Citations
Dr. Gilmartin believes endotoxin and exotoxin caused plaintiff's injury. p. 4, ¶ 5.	Tr. 1570, 1573, 1860	Dr. Gilmartins' opinion on causation is based upon temporal association and clinical story only.
Defendant has been aware of toxicity and the vaccine's capacity to cause brain damage, since 1960. p. 5, ¶ 6.	PX 19, 39, 41 42	Wyeth documents regarding vaccine improvements. No reference to brain damage.
Vaccine never modified since 1947. p. 5, ¶ 7.	Tr. 1102	Citation unrelated to proposition.
Wyeth understood how to make a safer vaccine in the fifties. p. 5, ¶ 6.	PX 96, 35, 66 41	No exhibit suggests Wyeth understood how to make a safer vaccine.
Known for 30 years that only exotoxin and "pillill are needed. p. 5, ¶ 8.	- - -	No citation.
Lederle's 1937 product is identical to the Japanese vaccine. pp. 5-6, ¶ 8.	- - -	No citation.
Wyeth executives believed acellular vaccine is "unmatched." p. 6, ¶ 8.	Tr. 436	Citation unrelated to proposition.
Lilly vaccine showed no serious reactions. p. 6, ¶ 9.	Tr. 943	Citation unrelated to proposition.

Wyeth executives described the epidemiological evidence regarding the Japanese vaccine as "stunning." p. 6, ¶ 8.	PX 80	Exhibit unrelated to proposition.
Wyeth admitted Lilly vaccine is safer. p. 6, ¶ 10.	PX 96, 36 Tr. 373-77	Citations contain no reference to Lilly vaccine.
Dr. Tint and Merck, Sharpe & Dohme had an extracted vaccine. pp. 6-7, ¶¶ 10-11.	PX 19, 663 Tr. 3055	Citations do not suggest that vaccine was an extracted vaccine.
Dr. Rubin and Dr. Long recommended Long's research be scaled up. pp. 7-8, ¶ 12.	PX 59B, 60A 60B, 61A, 63	No reference to scale up.
CNS disorders and strokes accompanied by brain damage are well known. p. 15, ¶ 25.	Tr. 873, 893-95, 1010 300-06, 248-49, 258-62, 298-99, 1441-43, 1449, 1453, 1473, 1512, 1521, 1570-74, 1589; PX 60A, 60B, 88G, 72, 88B, 149E, 149F, 682, 681, 679, 677, 683, 693, 173, 205, 238, 300, 302, 333, 376, 458, 557, 621, 641, 707, 711, 712, 173, 19B	Only 4 of plaintiff's 46 citations pertain to CNS disorders. Not one suggests how endotoxin could cause an occlusion in a blood vessel.
Wyeth package insert failed to advise of the presence of histamine sensitizing factors. p. 17, ¶ 29.	Tr. 807, 830	No reference to histamine sensitizing factors.
Wyeth routinely stored toxic lots or diluted them with passed lots. p. 17, ¶ 30.	Tr. 820-23, 197-99, 753,793-94, 884	No reference to toxic or diluted lots.
Wyeth should have autopsied mice brains. p. 18, ¶ 32.	– – –	No citation.
Failure to test during storage and handling. p. 19, ¶ 35.	Tr. 279, 493, 801	No reference to testing.
Toxicity test results depend on mouse strain. p. 19, ¶ 35.	– – –	No citation.
Plaintiff was normal between 2/2/80 - 3/17/80. p. 20, 2nd ¶.	Tr. 1142-46	Reference pertains to her condition before 2/2/80.

Dr. Gilmartin said plaintiff's stroke occurred within hours or days of her immunization. p. 25, 2nd ¶.	Tr. 543-44, 1674, 1706-1717	Text does not refer to association between stroke and immunization.
Dr. Gilmartin testified "in detail" regarding causal mechanism. p. 26, 2nd ¶.	– – –	No citation.
Four hours after the shot, Mrs. Graham called Dr. Hayes. p. 20, 4th ¶.	– – –	No citation.
Wyeth's documents state that its DTP contain 88.16 mg/ml endotoxin. p. 27, 2nd ¶.	DX 313, p. 5	Dr. Geier's documents, not Wyeth's. Does not say 88.16
Route of administering the vaccine is a non-issue. p. 27, 2nd ¶.	– – –	No citation.
Wyeth endotoxin levels are highest. p. 27, 2nd ¶.	– – –	Dr. Geier's endotoxin studies and testimony have been discredited.
Multiple effective and less reactive alternatives were available. p. 34, 1st ¶.	DX 228, 161; PX 258, 66, 72, 74, 128	Citations pertain to extracted vaccines shown to have a lower incidence of local reactions only or Japanese vaccine which could not have been available to plaintiff.
Dr. Gilmartin believed endotoxin in DTP enters blood and causes injury. p. 50, 3rd ¶.	Tr. 1835, 1660	No reference to causing injury.

STATEMENTS WHICH HAVE PARTIALLY INACCURATE CITATIONS IN SUPPORT.

Statement	Comments on Citation
The toxic effects of endotoxin and exotoxin have been well-known for over 40 years. p. 3, ¶ 3.	The citation to Tr. 248-49, a discussion of the effects of dermenocrotic toxin, and 258-62, a discussion of Lederle's pertussigen, have nothing to do with the asserted proposition. PX 19B, a patent, only discusses the necrotic effects of pertussis, which is not at issue. DX 161 and 44 pertain to the acellular vaccine and do not support the proposition.

The neurotoxicity of the pertussis vaccine is avoidable and poses an unacceptable and unreasonable danger of brain damage. p. 4, ¶ 4.	The following citations do not relate to the proposition: Tr. 262-67 (Dr. Zahalsky's unproven theories regarding alternative vaccine formulations); Tr. 371 (reflects that the vaccine should be toxoided by heating at 56°C., which is the process used by Wyeth); Tr. 375-77 (pertains to a literature report of an extracted antigen but no suggestion is made that this would result in a vaccine); Tr. 436 (concerns Wyeth's pursuit of an acellular vaccine which could not have been available to plaintiff); Tr. 786 (pertains to a report from Dr. Sato in 1979 well after Lot 66701 was made); PX 26 (a document reporting on a conference where toxicity was discussed); PX 19 (Dr. Tint's parabens patent which only suggests a method for accellerated detoxification) ; PX 19A (a patent which does not suggest that a feasible vaccine was obtainable).
Wyeth has acknowledged the need to reduce the toxicity through toxoiding exotoxin and removing of endotoxin. p. 5, ¶ 6.	The following citations are not supportive of the proposition: PX 53 (a Wyeth document requesting reactivation of a vaccine research project); PX 55 (correspondence from a Wyeth employee which makes no reference to reduced toxicity, exotoxin, or endotoxin.); PX 173 (a literature report, which is not a Wyeth document); Tr. 249 (testimony by Dr. Zahalsky which does not mention Wyeth); Tr. 298-99 (Dr. Zahalsky's discussion of a literature report which does not address Wyeth).
Dr. Tint admitted the necessity for reducing adverse reactions in his patent application. p. 7, ¶ 10.	PX 19—Dr. Tint commented only on fever and malaise.
Attribution of a statement to Dr. Tint that he had concluded a soluble pertussis product was available and that delays in marketing the product were strange. p. 7, ¶ 10.	Plaintiff fails to set forth the entire sentence in PX 35 which concludes, "[H)owever, there may be technical difficulties related to processing and testing which are not immediately obvious."
Dr. Long's extracted antigen repeatedly passed federal potency and toxicity tests, p. 8, ¶ 3.	The citations, Tr. 3002; PX 60, 61A established that Long's antigen passed only one test.
CDC information revealed that Wyeth whole-cell was reporting excessive reactions. p. 12, ¶ 21.	The only citation which pertains to the proposition is PX 105 which categorizes the number of abscesses and cases of SIDS by manufacturer. Neither reaction is involved in this case. The remaining citations, PX 88F, 88G, 88M; Tr. 209-10, have nothing to do with proposition.

The medical literature and Wyeth documents establish beyond doubt that the acute and highly lethal effects of pertussis vaccine are due to the presence of endotoxin and the adjuvant activity of exotoxin. p. 23, 2nd ¶.	The following citations are not supportive: PX 19 (Dr. Tint's Parabens patent which mentions fever and malaise without discussing specific toxins); PX 19A (a 1938 patent which actually suggests use of the toxic component and "poison-free" bacteria); PX 19B (1948 patent which mentions only necrosis as a toxic reaction) ; PX 26 (a Wyeth document pertaining to a conference where toxicity was discussed); PX 36 (a Wyeth document which does not mention endotoxin, exotoxin, or adverse reactions); PX 59 (an annual report, which describes the causation issue as "totally obscure"); PX 173 (a literature report which states "the mechanism whereby the encephalopathy is produced is not elucidated by the present study") ; PX 238 (a literature report involving brain wave changes following immunization but not suggesting what component of the vaccine is involved or how); PX 376 (a report prepared by a federally appointed panel of experts which does not discuss the causal mechanism or components of the vaccine).
Dr. Zahalsky, testified at length and in great detail, as to how endotoxin and DPT as a whole, cause injury in human beings. p. 26, 2nd ¶.	None of the citations offer any guidance on how endotoxin in DTP could cause an occlusion or blockage of the middle cerebral artery. The citations, Tr. 256, 266-75, 298-317, 342, 370-75, 431, 475, 488-90, 737, 772, 819, have nothing to do with the injuries in this case.

Although the full impact of the above listed misstatements of "fact" can only be garnered by a studied comparison of the arguments and the record, perhaps the flavor can be conveyed by the following examples.

1. Plaintiff states that "the medical literature and Wyeth documents established beyond doubt that the acute and highly lethal effects of pertussis vaccine are due to the presence of endotoxin and the adjuvant activity of exotoxin," citing, in part, PX 173 and PX 59. (Apee. Br. 22-23.) PX 173 is a journal article which concludes, "The mechanism whereby the encephalopathy is produced is not elucidated by the present study." PX 59, a Wyeth document, states: "The cause of

this very serious complication which occurs both with vaccination and disease itself is totally obscure."

2. Plaintiff cites DX 503 to support a statement that stroke is an encephalopathy, which is a well-known DTP reaction. (Apee Br. 24.) DX 503 is a published compilation of reports of possible adverse reaction received by the CDC which, in fact, shows that the number of reports received of "encephalopathy" was no greater than would be expected from chance alone; the entire report never mentions stroke.

3. Plaintiff says that "(t)he FDA informed Wyeth that it would license an acellular vaccine with minimal cooperation required from Wyeth." (Apee Br. 34.) One of her citations, PX 74, in fact, states: "Drs. Robbins and Manclark (of the FDA) indicated that they cannot offer any specific recommendations as to how to make a better vaccine."

4. Although argued in terms of encephalopathy and not stroke, plaintiff alleges that PX 713 supports the conclusion that endotoxin in the DTP can cause encephalopathy. This is a grossly misleading statement.[1]

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1. Plaintiff asserts that only five nanograms of endotoxin per mililiter are required to cause brain damage, citing a letter (PX 713) to a Wyeth expert which inaccurately reported that Dr. Zahalsky so testified based on a study by Wolf. (Apee. Br. 27.) In fact, Dr. Zahalsky did not so testify. All that Dr. Zahalsky testified was that according to Wolf's study, *which did not even involve Bordetella pertussis endotoxin* (i.e., the endotoxin in DTP), five nanograms per kilo of body weight would produce *fever, not brain damage.* (Tr. 633-35.)